REMARKS

Re-examination and reconsideration of the subject application, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

First, Applicant would like to thank Examiner Seharaseyon and his Supervisor for discussing the present application with Applicant's representatives on December 20, 2004.

As noted in the Office Action Summary, claims 1-5, 8-16, and 20 are pending in the application. Claims 8 and 20 are amended herein to address issues of grammar. No new matter is added by way of the present Amendment.

Applicant acknowledges with appreciation that the rejection of claims 1-5, 8-16, and 20 under 35 U.S.C. § 112 has been withdrawn. Applicant further acknowledges with appreciation that the rejection of claims 1-5 and 10-16 under 35 U.S.C. § 103(a) based on Goren et al. in view of Zahorska et al. has been withdrawn.

Rejections under 35 U.S.C. § 103 rejection

Goren et al. in view of Johnston

Claims 1-4, 8, 9, 10-13, and 20 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Goren et al. (1986) ("Goren") in view of Johnston (U.S. Patent No. 4,780,413) ("Johnston"). Applicant traverses the rejection.

For a *prima facie* case of obviousness, the following three requirements must be met. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or

incentive that would have motivated the skilled artisan to modify a reference or to combine the reference with another reference. Second, the proposed modification must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. Third, the prior art reference must teach or suggest all the limitations of the claims. The teachings or suggestions as well as the expectation of success must come from the prior art and not from applicant's disclosure. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988); *Amgen, Inc. v. Chugai Pharm. Co.,* 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991); and *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991). Applicant respectfully submits that these criteria have not been met in the present Office Action.

First, the references fail to provide motivation to arrive at the present invention or an expectation of success. As in the previous Office Action, Goren et al. is cited as the primary reference for purportedly disclosing a process to produce interferon-α in human lymphocytes, and purportedly using human peripheral blood lymphocytes to produce interferon-α by inducing them with Sendai virus. The Office argues that it would have been obvious to the skilled artisan to enhance the interferon production following the induction with a virus of human lymphocytes, as described by Johnston. Applicant respectfully disagrees.

In the present Office Action, on page 3, the Office states that Johnston as the secondary reference was cited to "teach increased production of interferon-α following the induction of leukocytes with virus and the subsequent treatment of infected cells..." [emphasis added]. Furthermore, according to the Office, the Johnston reference states that "primary human white blood cells cannot provide

abundant amounts of interferon-α", and that it is concerned with solving this problem through use of an enhancing agent. However, Applicant submits that Johnston does not disclose these elements. Johnston has been misinterpreted. Thus, Johnston does not remedy the deficiencies of Goren.

(a) Johnston uses lymphoblastoid cells, not leukocytes, and teaches away from the use of leukocytes

The Johnston reference teaches how to increase the production of interferon-α (IFN-α) in cell lines of transformed human cells, namely lymphoblastoid cells. In contrast, the present claims are directed to IFN-α production in untransformed leukocytes, *i.e.* primary white blood cells.

The primary leukocytes of the present invention and the lymphoblastoid cells of Johnston have important differences with regard to the claimed invention. In the outstanding Office Action, the Office posits that both lymphoblastoid cells and peripheral human blood leukocytes produce interferon-α following viral induction of the cells. However, the Applicant submits that there are key differences between the cells used in Johnston and those used in the present invention. These differences are predicated on the fact that the cells of the present invention are primary, untransformed cells. In contrast to the leukocytes of the claimed invention, the lymphoblastoid cells of Johnston are 1) transformed; 2) from an immortal cell line; and 3) derived from neoplastic tissue. These differences are such that the skilled artisan would not expect the same or even a positive result, or be motivated to modify the cited references to arrive at the claimed invention.

(a)(1) The cells of Johnston are transformed

The *Dictionary of Cell Biology* (2d Ed., Lackie and Dow (1995) New York: Academic Press, page 364; copy of definition attached) defines the "transformation" of cells as "[a]ny alteration in the properties of a cell that is stably inherited by its progeny...Transformation can be recognized by changes in growth characteristics, particularly in requirements for macromolecular growth factors, and often also by changes in morphology." The cells of Johnston are transformed cells. In contrast, the cells of the present invention are untransformed, primary cells. The *Dictionary of Cell Biology,* page 292, defines "primary cell culture" as "[o]f animal cells, the cells taken from a tissue source and their progeny grown in culture before subdivision and transfer to a subculture." Thus, the cells of the present invention have not undergone transformation and therefore are not subject to the problems associated with transformed cells.

These problems, characteristic to transformed cells, are relevant to the present invention, and the reason why Applicant chose to use primary, untransformed cells. For example, once properties of cells are lost in culture, it is very difficult to relate the cultured cells to actual functional cells in the tissue from which the cell culture is derived. In support, Applicants submit herewith material from *Culture of Animal Cells: A Manual of Basic Technique* (Freshney (2000) New York: John Wiley & Sons, Inc.). This book is a well known reference known in the art for cell culture. Page 5, second column, notes under "Origin of Cells", that "[i]f differentiated properties are lost, for whatever reason, it is difficult to relate the cultured cells to functional cells in the tissue from which they were derived."

Page 6 goes on to state that "[i]nstability is a major problem with many continuous cell lines, resulted from their unstable aneuploid chromosomal constitution....Many of the differences in cell behavior between cultured cells and their counterparts *in vivo* stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of the histology of the tissue are lost, and as the cells spread out, become mobile, and, in many cases, start to proliferate, so the growth fraction of the cell population increases."

Page 17 discusses transformation of cells, noting "[t]he term *transformation* has been applied to the process of formation of a continuous cell line partly because culture undergoes morphological and kinetic alterations, but also because the formation of a continuous cells line is often accompanied by an increase in tumorigenecity." Page 259, in Chapter 16, discusses the concept of differentiation in the context of cell culture, "[t]he phenotype of cells cultured and propagated as a cell line is often different from the characteristics that predominate the tissue from which it was derived."

Applicants also refer to Chapter 17, entitled "Transformation". It is stated on page 269 that "[t]ransformation is seen as a particular event or series of events that depends on and promotes genetic instability. It alters many of the cell line's properties, including growth rate, mode of growth, specialized product formation, longevity, and tumorigenicity."

In light of these changes in properties that occur when cells are transformed, the skilled artisan cannot extrapolate from the transformed cells of the cited

references to the untransformed cells of the present invention and expect the same result.

(a)(2) The cells of Johnston are immortalized

The change in properties occurring when a cell is immortalised leads to a large variation in properties. Thus, the fact that the cell line of Johnston is an immortal cell line also imparts instability to the cells, as compared to the primary cells of the present invention. *Culture of Animal Cells: A Manual of Basic Technique* states, on page 273, that with regard to immortalization, "[i]t must be assumed, however, that some aspects of growth control are abnormal and there is a likely increase in genomic instability. Furthermore, immortalized cell lines often lose the ability to differentiate".

(a)(3) The cell line of Johnston is derived from a tumor

It has long been well established that the approximately 200 different cell types in multicellular vertebrates show clear differences in gene expression, reaction to external stimuli, and internal homeostasis. Therefore, there are very few factors which have a generalized effect on gene expression. Many of the previously used substances, prior to the present invention, acted on signaling pathways involved in cellular networks, which are unique for each cell type. Furthermore, most cell lines are derived from malignant tumors, with dysregulated gene expression. This may result in the opening of a new signaling pathways or in the closing of signaling pathways. Therefore, inference and extrapolation from tumor cells to normal cells is random and not relevant.

This is especially relevant with regard to Johnston, because its results are obtained in Namalwa/WRL cells. The results would also be expected in other Namalwa sublines (*see* Johnston column 2, lines 52-55). Namalwa cells were originally established from the tumor mass of an African child with Burkitt's lymphoma in 1967. The skilled artisan is well aware that Burkitt's lymphoma cells have a chromosomal rearrangement, several mutated genes, and moreover carry the Epstein-Barr Virus (EBV) genome. (*See* attached abstract from the DSMZ-Deutsche Sammlung von Mikroorganismen und Zellkulturen GmbH on the NAMALWA cell line (1969)).

Culture of Animal Cells: A Manual of Basic Technique, page 17, discusses transformation of cells, noting "[t]he term *transformation* has been applied to the process of formation of a continuous cell line partly because culture undergoes morphological and kinetic alterations, but also because the formation of a continuous cells line is often accompanied by an increase in tumorigenecity. A number of the properties of continuous cell lines, such as reduced serum requirement, reduced density limitation of growth, growth in semisolid media, aneuploidy...and more, are associated with malignant transformations".

Thus, the cells of the Johnston reference are very dissimilar to the primary (untransformed) human leukocytes of the present invention. The skilled artisan has no expectation of success in applying the substances of the Johnston reference to human untransformed leukocytes. The limited applicability of the Namalwa results is also evident, because the Johnston reference only discloses that the invention may be applied to other sub-lines of Namalwa cells and other "suitable" lymphoblastoid cells (*see* Johnston column 2, lines 52-55).

Therefore, there are significant differences between the cell system of the present invention and those of the cited references, dependent on differences in cell growth, differentiation, neoplastic potential and cell type. To this end, Johnston states that primary cells, such as the cells from the presently claimed invention, cannot provide abundant amounts of IFN-α, as discussed in more detail below.

In fact, Johnston teaches away from the use of leukocytes. The totality of the prior art must be considered, and proceeding contrary to accepted wisdom in the art is evidence of nonobviousness. *In re Hedges,* 783 F.2d 1038, 228 USPQ 685 (Fed. Cir. 1986). To this end, Johnston states that primary cells cannot provide abundant amounts of IFN-α. This is why the use of primary cells is not taught or suggested by Johnston. Additionally, Johnston undermines motivation to attempt it with untransformed cells for this reason.

After stating, in column 1, lines 17-28, that primary cells cannot provide abundant amounts of IFN-α, and that cell lines of transformed, lymphoblastoid cells are used instead of primary cells, Johnston proceeds to discuss how to increase the production of IFN-α from such transformed lymphoblastoid cells. Thus, Johnston leads the skilled artisan away from the claimed invention, instructing them to use lymphoblastoids (*i.e.*, transformed lymph cells) and not to use primary cells, as with the present invention. Not only does Johnston, combined with Goren, fail to provide the skilled artisan with an expectation of success or motivation to arrive at the present invention, it even teaches away from the present invention.

Thus, in contrast to the Examiner's interpretation, the Johnston reference is not directed to increasing the production of IFN-α in leukocytes, and cannot even be extrapolated to arrive at the present invention.

b) Johnston does not disclose the use of enhancing agents to enhance production in leukocytes

In fact, Johnston reference is silent about use of an enhancing agent to enhance production of IFN-α in leukocytes. The fact that the teaching of Johnston is directed exclusively towards IFN-α production in lymphoblastoid cell lines is evident throughout, *e.g.,* in the recited experiments and in the entire discussion from column 1, line 17 to column 2, line 6.

There is no motivation to modify the teachings of Goren combined with Johnston for the claimed purpose, let alone is there an expectation that such a modification (*i.e.*, the use of leukocytes instead of lymphoblastoids) would be successful. Thus, Goren in view of Johnston fails two of the three requirements for evincing a *prima facie* case of obviousness.

Applicants now turn to the third requirement for finding obviousness: teaching the limitations of the claims. This will be addressed claim-by-claim.

Claim 1

The last requirement that each of the limitations of the claims be taught by the reference also is not met. Claim 1 of the present invention is directed to a process for the production of α-interferon comprising the steps of inducing human leukocytes by means of a virus, treating the leukocytes with an enhancing agent selected from: a) xanthine, pyrimidinol and pyrimidinone, theophylline, theobromine, enprophylline, hypoxanthine, 8-phenyltheophylline, 2-amino-5-bromo-6-methylpyrimidinol, 2-amino-6-methyl-4-pyrimidinol and thymine; b) an enhancing agent which is an organic solvent, selected from the group consisting of non-aromatic ketones,

aliphatic or cyclic amides, alkylated aliphatic or cyclic urea derivatives and aliphatic or cyclic sulfoxides; or a combination of the compounds from a) with an organic solvent from b). There elements are not recited by the combination of Goren with Johnston, and as discussed in detail above, the use of lymphoblastoid cells of the cited reference does not lead to the use of leukocytes, as with the claimed invention.

Claim 2

The elements of claim 2, which is dependent on claim 1, are also not taught, and thus the method recited in Claim 2 is nonobvious for the reasons previously cited for claim 1. In addition, there is no mention in Johnston of the use of monocytes as the induced cells. Further to the above discussion of the differences between leukocytes and lymphoblastoids, Applicants note that the differences between the cells of the cited references and monocytes are even more stark. In fact, monocytes are not even derived from the same cells as lymphoblastoids. In support, Applicants submit herewith Figure 2-8 from *Immunology, Immunopathology & Immunity*, 5th Ed. Sell (1996) Stamford, Connecticutt: Appleton & Lange, pages 41-42. As shown, the lymphoid cell development is not related to the hemocytoblasts, mono-myeloblasts and promonocytes iterations which eventually become monocytes.

Claim 3

Claim 3 depends on claim 1, further reciting that the enhancing agent is added at the same time or up to 4 hours after the virus induction. Thus, the cited references fail to

recite the elements of claim 3, as claim 3 is nonobvious for the reasons previously cited for claims 1 and 2.

Claim 4

The method recited in Claim 4 is nonobvious for the reasons previously cited for Claims 1 and 2. Claim 4 is directed to the process of claim 1, wherein the virus is Sendai virus.

Claims 8-9

The methods recited in claims 8 and 9 are nonobvious for the reasons previously cited for Claim 1. Claims 8 and 9 are directed to a process for the production of α-interferon comprising the steps of inducing human leukocytes by means of a virus, and treating the leukocytes with an enhancing agent selected from xanthine, pyrimidinol and pyrimidinone, theophylline, theobromine, enprophylline, hypoxanthine, 8-phenyltheophylline, 2-amino-5-bromo-6-methylpyrimidinol, 2-amino-6-methyl-4-pyrimidinol and thymine; or an enhancing agent which is an organic solvent selected from the group consisting of acetone, 2-butanone, 1,3-dimethyl-2-imidazolidinone, dimethylsulfoxide, N-ethyl-2-pyrrolidinone, 4-methyl-2- pentanone, N-methyl-2-pyrrolidinone, 2-pyrrolidinone, tetramethylene sulfoxide, and N,N-dimethylacetamide; or a combination of the compounds from a) with an organic solvent from b). Claim 8 recites the specific solvent, N-methyl-2-pyrrolidinone.

Claims 10-13

The method recited in claims 10-13 are nonobvious for the reasons previously cited for claims 1 and 2. Claim 10, which depends from claim 2, recites that the enhancing agent is added at the same time or up to 4 hours after the virus induction. Claims 11-13, which depend from claims 2, 3, and 10 respectively, recite that the virus is the Sendai virus, as with claim 4.

Claim 20

The method recited in Claim 20 is nonobvious for the reasons previously cited for claims 1 and 2. Claim 20, as dependent on claim 2, is directed to the organic solvent as any of acetone, 2-butanone, 1,3-dimethyl-2-imidazolidinone, dimethylsulfoxide, N-ethyl-2-pyrrolidinone, 4-methyl-2- pentanone, N-methyl-2-pyrrolidinone, 2-pyrrolidinone, tetramethylene sulfoxide or N,N-dimethylacetamide.

As the cited references do not recite each and every element of the claimed invention, a case of prima facie obviousness has not been adduced.

Further, Applicants respectfully submit that unexpected results are in fact present with respect to the claimed methods.

It is a well established legal precedent that the presence of an unexpected, advantageous or superior result is evidence of nonobviousness. *See* M.P.E.P. § 716.02(a); *In re Papesch*, 315 F.2d 381, 137 U.S.P.Q. 43 (C.C.P.A. 1963). Along these lines, it is also well established that "a greater than expected result" is evidence of nonobviousness. *See* M.P.E.P. § 716.02(a); *In re Corkill*, 711 F.2d 1496, 226 U.S.P.Q. 1005 (Fed. Cir. 1985).

As even set forth in the cited reference, Johnston, it was understood in the art that primary cells cannot provide abundant amounts of IFN-α. Thus, the skilled artisan is encouraged to use cell lines of transformed, lymphoblastoid cells and not to use primary cells. However, it was unexpectedly found by the inventor that primary leukocytes could in fact be used with the claimed enhancing agents to produce abundant amounts of IFN-α. The use of primary, untransformed cells was previously thought to be ineffective at producing IFN-α. However, the use of primary cells, as opposed to the use of transformed cells, is highly advantageous, as it avoids the problems associated with transformed cells and cell lines derived from tumors, discussed in detail above. These problems include instability and loss of functional characteristics.

Response to specific comments in Office Action

Applicant now addresses specific comments in the outstanding Office Action regarding this rejection. On page 3 of the outstanding Office Action, the Examiner notes that Johnston "in both EP No: 0097353 and U.S. Patent No. 4,780,413 (see Table II) show conflicting results with respect to the stimulatory effect of sodium butyrate". Applicant states this is not the case. With regard to the Examiner's reading of Example 2 and Table II of Johnston, the Applicant respectfully points out that the results shown are not conflicting, and that it is not disputed in the art that IFN-α production by cell lines of lymphoblastoid cells can be stimulated by pre-treatment with sodium butyrate. In fact, Johnston discloses as much in column 5, lines 5-16, referring to EP 000 520 and EP 008 391.

Careful reading of the cited Example shows that Table II merely shows the effect of the various enhancers tested, with or without pre-treatment with sodium butyrate. The effect of sodium butyrate alone is not studied. The final column of Table II relates to increase in IFN titer relative to control without enhancer. The results in the first six rows of the table are compared to a control obtained without pre-treatment with sodium butyrate (row 1), whereas the results in the last six rows of the table are compared to a control obtained with pre-treatment with sodium butyrate (row 7). Thus, the table shows the results from two sets of samples that each have their own, individual control (the controls being shown in rows 1 and 7, respectively). This Example gives no quantitative data to enable a comparison between production in the presence versus the absence of sodium butyrate, and so it does not show the allegedly conflicting results. As a consequence, the Applicant submits that the statement on page 4, line 34 to page 5, line 16 of the present specification is valid, and shows that the behavior of transformed lymphoblastoid cells is not indicative or predictive for the behavior of primary white blood cells or leukocytes in terms of IFN-α production.

In summary, it is submitted that Goren et al. combined with Johnston fail to render the claimed invention obvious because there is insufficient motivation to modify Johnston. There is no reasonable expectation of success of achieving the claimed method when modifying Johnston. Johnston actually teaches away from the claimed method and the two references in combination fail to teach or suggest each and every element recited the present claims. Goren alone and Johnston alone have deficiencies that the other reference taken with it fails to cure. Applicant respectfully requests withdrawal of this rejection.

Goren et al. in view of Johnston and Slattery et al.

Claims 5 and 14-16 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Goren et al. (1986) in view of Johnston (U.S. Patent No. 4,780,413) and Slattery et al. (*J. Gen. Virol.*, 1980, 49:91-96).

Claims 5 and 14-16 depend from claims 1, 2, 3, and 4, respectively. Therefore, what is stated above regarding the combination of Goren et al. and Johnston also applies here in terms of the rejection of these claims. In so far as the Examiner interprets the Slattery et al. reference to provide the missing claim features for establishing a *prima facie* obviousness case or to overcome the deficiencies of Johnston and Goren et al., the Applicant traverses the rejection.

The study reported in Slattery et al. relates to the production of mouse interferons of an unspecified type by Ehrlich ascites tumour cells (EAT cells). As is known by the person of skill in the art, EAT cells are murine carcinoma cells (transformed cells) (*see* ATCC CCL-77, Erlich-Lettre Ascites, strain E, from ATCC Cell Lines and Hybridomas, 8th Ed. (1994) American Type Culture Collection, page 45, attached hereto). For the purposes of the present invention, EAT cells bear no resemblance in structure or function to the untransformed human leukocytes used in the process as presently claimed. EAT cells are not leukocytes; they are murine in nature and not human cells, and thus EAT cells do not make human interferon-α. Applicant submits that the skilled person would not have any motivation to apply the teaching of Slattery et al. to a system of production that uses human leukocytes, and much less any reasonable expectation of success. Thus, alone, Slattery fails to

teach the claimed invention. Slattery further fails to remedy the deficiencies of Goren and Johnston discussed previously.

Thus, the combination of these three references fails to describe all the elements of the independent claim, at least for the reason that none of them teaches treating leukocytes with an enhancing agent. Furthermore, the Applicant submits that the combination of them amounts to using hindsight to pick and choose between references, and that the skilled person at the date of priority of the present patent application would have had no motivation to combine the references. For at least these reasons, the Applicant maintains that no *prima facie* case for obviousness has been established, and respectfully requests that this rejection under 35 U.S.C. § 103 be withdrawn.

CONCLUSION

From the foregoing, further and favorable action in the form of a Notice of Allowance is respectfully requested and such action is earnestly solicited.

In the event that there are any questions concerning this amendment or the application in general, the Examiner is respectfully requested to telephone the undersigned so that prosecution of the application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

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By: _____
Deborah H. Yellin
Registration No. 45,904

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

VA 555536.1